The Claims

What is claimed is:

1. A method of treating cancer or a bacterial or protozoal infection comprising the adjunctive administration to a mammalian subject in need of such treatment of a pharmaceutically effective amount of a macrolide antibiotic and a pharmaceutically effective amount of a Substance P antagonist.

2. The method of claim 1 wherein the subject is a companion animal or human.

3. The method of claim 1 wherein the macrolide antibiotic is selected from the group consisting of erythromycin, clarithromycin, azithromycin, josamycin, and tylosin.

4. The method of claim 1 wherein the Substance P antagonist is selected from the group consisting of:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluromethoxylphenyl)piperidine;
(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
(2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
(2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxyphenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;
(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;
(2S,3S)-3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
(2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxybenzyl)]aminopiperidine;
(2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)aminopiperidine;
3-[N-(2-methoxy-5-trifluoromethoxybenzyl)-amino]-5,5-dimethyl-2-phenylpyrrolidine;
3-[N-(2-methoxy-5-trifluoromethoxybenzyl)-amino]-4,5-dimethyl-2-phenylpyrrolidine;
3-(2-cyclopropyloxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(2-cyclopropylmethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(2-difluoromethoxy-5-phenylbenzyl)amino-2-phenylpiperidine;
3-(5-cyclopropylmethoxy-2-difluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;
3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;
2-phenyl-3-(5-n-propyl-2-trifluoromethoxybenzyl)amino-piperidine;
3-(5-isopropyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(5-ethyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(5-sec-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
3-(5-difluoromethoxy-2-methoxybenzyl)amino-2-phenylpiperidine;
3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpyrrolidine;
3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylhomopiperidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxy-benzyl)aminopyrrolidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxy-benzyl)aminohomopiperidine;

3-[2,5-bis-(2,2,2-trifluoroethoxy)benzyl]amino-2-phenylpiperidine;

2-phenyl-3-(3-trifluoromethoxybenzyl)aminopiperidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminopiperidine;

1-(5,6-difluorohexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

1-(6-hydroxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-phenyl-4-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-azabicyclo[3.3.0]octane;

4-benzhydryl-5-(2-methoxy-5-trifluoromethoxybenzyl)amino-3-azabicyclo[4.1.0]heptane;

4-(2-methoxy-5-trifluoromethoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane;

2-phenyl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine;

9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-8-amine;

9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-3-thia-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-8-amine;

8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine;

5,6-pentamethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

5,6-trimethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

9-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-3-oxa-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-3-amine;

8-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-7-azatricyclo[4.4.1.$0^{5,10}$]undecan-9-amine; and

2-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-1-azabicyclo[3.2.2]nonan-3-amine;

and pharmaceutically acceptable salts and solvates thereof.

5. The method of claim 4 wherein the Substance P antagonist is (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine, or a pharmaceutically acceptable salt or solvate thereof.

6. A method of preventing or treating emesis associated with a macrolide antibiotic comprising administering to a subject in need of such prevention or treatment a pharmaceutically effective amount of a Substance P antagonist.

7. The method of claim 6 wherein the subject is a companion animal.

8. The method of claim 6 wherein the subject is a human.

9. The method of claim 6 wherein the Substance P antagonist is selected from the group consisting of:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-triflurомethoxylphenyl)piperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxyphenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;

(2S,3S)-3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxybenzyl)]aminopiperidine;

(2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)aminopiperidine;

3-[N-(2-methoxy-5-trifluoromethoxybenzyl)-amino]-5,5-dimethyl-2-phenylpyrrolidine;

3-[N-(2-methoxy-5-trifluoromethoxybenzyl)-amino]-4,5-dimethyl-2-phenylpyrrolidine;

3-(2-cyclopropyloxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-cyclopropylmethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-difluoromethoxy-5-phenylbenzyl)amino-2-phenylpiperidine;

3-(5-cyclopropylmethoxy-2-difluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

2-phenyl-3-(5-n-propyl-2-trifluoromethoxybenzyl)amino-piperidine;

3-(5-isopropyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(5-ethyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(5-sec-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(5-difluoromethoxy-2-methoxybenzyl)amino-2-phenylpiperidine;

3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpyrrolidine;

3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylhomopiperidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxy-benzyl)aminopyrrolidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxy-benzyl)aminohomopiperidine;

3-[2,5-bis-(2,2,2-trifluoroethoxy)benzyl]amino-2-phenylpiperidine;

2-phenyl-3-(3-trifluoromethoxybenzyl)aminopiperidine;

2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminopiperidine;

1-(5,6-difluorohexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

1-(6-hydroxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-phenyl-4-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-azabicyclo[3.3.0]octane;

4-benzhydryl-5-(2-methoxy-5-trifluoromethoxybenzyl)amino-3-azabicyclo[4.1.0]heptane;

4-(2-methoxy-5-trifluoromethoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane;

2-phenyl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine;

9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-8-amine;

9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-3-thia-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-8-amine;

8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine;

5,6-pentamethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

5,6-trimethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;

9-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-3-oxa-10-azatricyclo[4.4.1.$0^{5,10}$]undecan-3-amine;

8-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-7-azatricyclo[4.4.1.$0^{5,10}$]undecan-9-amine; and

2-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-1-azabicyclo[3.2.2]nonan-3-amine;

and pharmaceutically acceptable salts and solvates thereof.

10) The method of claim 9 wherein the Substance P antagonist is (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine, or a pharmaceutically acceptable salt or solvate thereof.

11) A pharmaceutical composition comprising a pharmaceutically effective amount of a macrolide antibiotic, a pharmaceutically effective amount of a Substance P antagonist, and optionally, a carrier.

12) The pharmaceutical composition of claim 11 wherein the carrier is an excipient.

13) The pharmaceutical composition of claim 11 wherein the macrolide antibiotic is selected from the group consisting of erythromycin, clarithromycin, azithromycin, josamycin, and tylosin; and the Substance P antagonist is (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine, or a pharmaceutically acceptable salt or solvate thereof.

14) The pharmaceutical composition of claim 11 wherein said pharmaceutical composition is suitable for oral, rectal, parenteral, transdermal, buccal, nasal, sublingual, or subcutaneous administration.

15) A method of treating cancer comprising the adjunctive administration to a mammalian subject in need of such treatment of a pharmaceutically effective amount of a macrolide antibiotic and a pharmaceutically effective amount of a Substance P antagonist.